



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assessment report

for

FABRAZYME

agalsidase beta

**Assessment report on the shortage of Fabrazyme'
Overview of Shortage Period: Spontaneous Reports from June 2009 through 15
September 2010 and Registry Data from June 2009 through 05 August 2010**

EMA/H/C/000370



I. INTRODUCTION

Fabry's disease is a lysosomal storage disorder due to a deficiency in alpha-galactosidase A. The natural course of the disease is illustrated in figure 1.

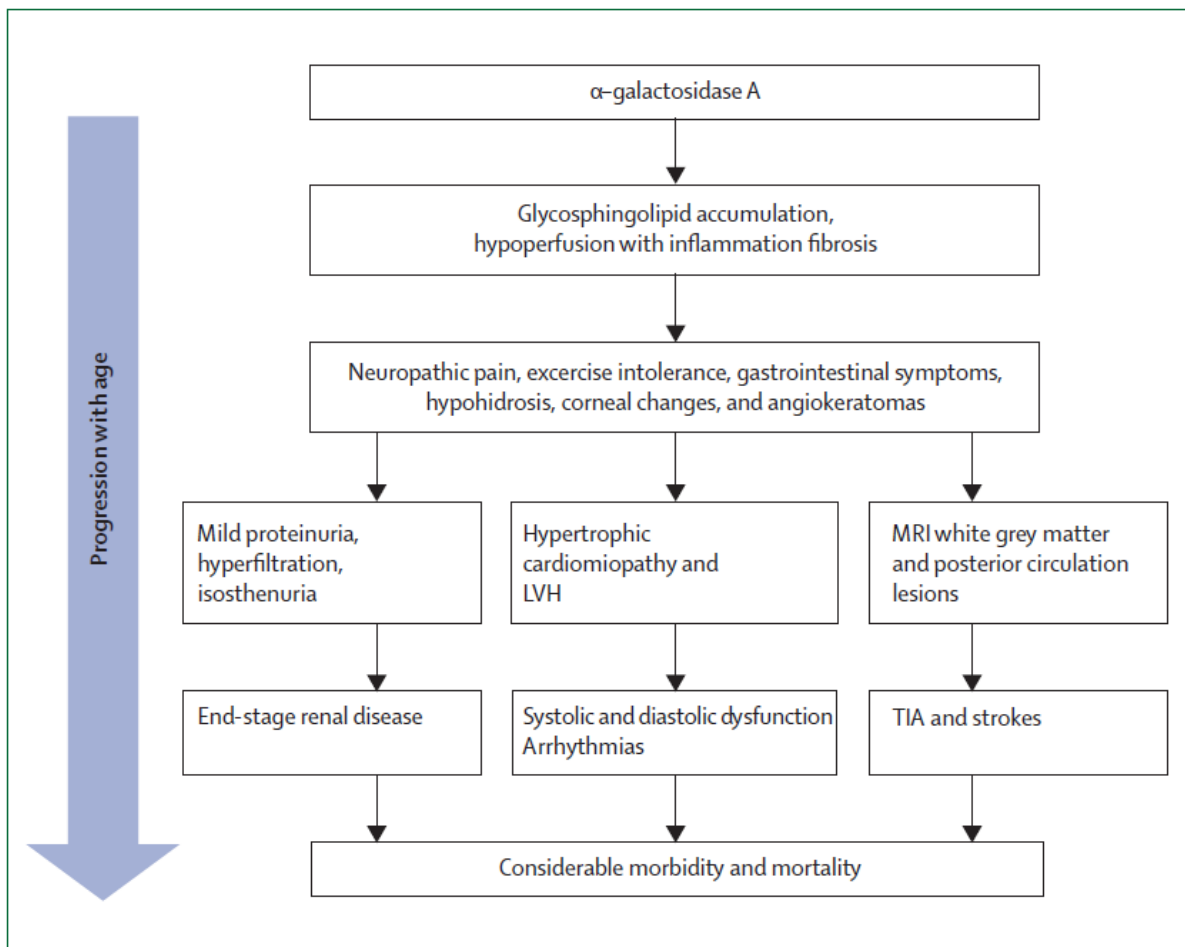


Figure 1: Progression of clinical findings in Fabry's disease with age

Progression of any of the paths depicted can proceed independently from the others, which means that for some patients, cardiac disease will be the most severe whereas for others renal or CNS disease can predominate. LVH=left ventricular hypertrophy. TIA=transient ischaemic stroke.

(Zarate & Hopkin. Lancet 2008;372:1427-35)

At the start of the disease (during the first decades of life), the main manifestations are pain (crises) and gastrointestinal symptoms. The long-term progression of Fabry disease is associated with chronic renal disease, cardiovascular disease, and cerebrovascular events (during fifth decade of life); this deterioration is a major cause of morbidity and mortality.

Fabrazyme® is an enzyme replacement therapy for Fabry's disease. The recommended dose and frequency in section 4.2 of the SmPC is 1 mg/kg every other week (eow).

Since June 2009 there has been a shortage of supply of Fabrazyme (agalsidase beta) because of production and quality (GMP) problems. To date four Direct Healthcare Professional Communications (DHPCs) with dose recommendations have been released in the European Union (EU):

25 June 2009:

- Children and adolescents less than 18 years old as well as adult male Fabry patients to continue with recommended Fabrazyme dosing and frequency.
- Adult female Fabry disease patients with no evidence of clinically significant end organ damage to be treated with a reduced dose of 0.3-0.5 mg/kg every 2 weeks.

28 September 2009:

- Children and adolescents less than 18 years old to continue with recommended Fabrazyme dosing and frequency.
- Adult male patients already treated and stabilized to receive 0.3 mg/kg every 2 weeks (as for adult female patients).
- Patients should be followed up every two months, and plasma or urinary globotriaosylceramide (GL-3) levels should be closely monitored.
- Patients who demonstrated a deterioration of disease should be switched back to their original dosage regimen with Fabrazyme.

22 April 2010:

- Treatment recommendations as communicated in the DHPC of September 2009 remained in place.
- For patients experiencing aggravation of disease symptoms and/or AEs ascribed to the lowered dose of Fabrazyme, physicians were advised to switch their treatment back to their original dosing regimen or initiate treatment with an alternative approved medicinal product.

09 July 2010:

- No new patients should be started on Fabrazyme, if alternative treatment is available.
- For patients on a dose lower than the recommended dose, physicians should consider switching to an alternative treatment, such as Replagal.
- Where alternative treatment is not available or where (continuation of) treatment with Fabrazyme is deemed medically necessary, it is important to note that an increase in clinical manifestations indicative of Fabry disease progression has been observed with the lowered dose.

In the United States all patients were asked to reduce their Fabrazyme use by spreading out their usual dose over a longer period of time.

During the shortage period, the MAH has updated the Rapporteur with reports on spontaneous reporting and data from the Fabry registry. These data and the Rapporteur's conclusions are summarized in this assessment report.

On 4 and 9 October 2010 a consensus meeting took place of representatives of physicians treating Fabry disease in the EU. At that meeting treatment recommendations in times of shortage were agreed. A representative of the EMA was present as an observer.

The purpose of this assessment report is to present an overview of the data received so far on patients on a lower dose of Fabrazyme.

II. POSSIBLE DETERIORATION IN PATIENTS ON THE LOWERED DOSE

The Rapporteur has reviewed all data from spontaneous reports regarding patients who reported adverse events (AEs) assessed to be suggestive of clinical deterioration on a lowered dose of Fabrazyme (from Genzyme's Global Patient Safety and Risk Management department (GPS&RM) database) for the period from 25 June 2009 through 15 September 2010.

In addition, all information from the Fabry Registry regarding certain clinical characteristics of patients whose doses of Fabrazyme were lowered during a period of approximately 13 months, from 25 June 2009 through 05 August 2010 have been reviewed and the data from both sources have been compared.

In all cases, it was assumed that these patients' doses were lowered in response to the reduction in the global supply of Fabrazyme during this period.

The MAH considered the following:

A. All spontaneous cases reported to GPS&RM and medically reviewed from 25 June 2009 through 15 September 2010 were considered for the analysis of patients experiencing clinical deterioration on a lower dose of Fabrazyme if they met the following three criteria:

1. The reported AE occurred after 25 June 2009,
2. The patient was on a lowered dose of Fabrazyme due to the supply shortage, and
3. The AE was not an infusion associated reaction (IAR).

B. After selecting the cases that met these criteria, the narratives were screened by the MAH for information with regard to evidence of clinical deterioration. A medical review of these cases, which included all relevant medical history and available laboratory data, was performed by GPS&RM to determine whether the AEs were suggestive of potential clinical deterioration. Due to the ongoing limited supply, cases of patients with clinical deterioration but without complete documentation of a lowered dose have also been incorporated into the reports; further efforts are being made with the patient's health care professional (HCP) to confirm the dose reduction in these cases.

C. Events assessed to be suggestive of potential clinical deterioration after medical review included, but were not limited to: cardiovascular events such as arrhythmia, coronary artery disease or heart failure; cerebrovascular events such as transient ischaemic attacks or cerebrovascular accidents; renal events such as renal impairment or renal failure; gastrointestinal events such as abdominal pain, nausea, vomiting, and diarrhoea; events consistent with Fabry disease-related pain such as paraesthesias, pain in extremities, or peripheral neuropathy; changes in hearing; and constitutional symptoms such as fatigue and malaise.

Physicians who enrol patients in the Fabry Registry are asked to monitor patients and submit clinical data according to a Minimum Recommended Schedule of Assessments. This schedule includes key clinical and laboratory parameters that should be evaluated and the frequency at which they should be reported to the Fabry Registry. However, Genzyme has found that these data are typically entered on a semi-annual or annual basis. In addition, not all changes in dosage have been reported to the Fabry Registry and changes in the average reported dose may not accurately reflect patients' actual treatment regimens.

Events of chronic renal disease, cardiovascular disease, cerebrovascular events, and deaths reported to the Fabry Registry were investigated in patients whose doses were lowered during the period from 25 June 2009 through 05 August 2010. In addition, data related to peripheral pain, abdominal pain, and diarrhoea were included. Reported plasma and urine levels of GL-3 were also analyzed in patients who are enrolled in the Fabry Registry.

III. REVIEW OF DATA FROM SPONTANEOUS REPORTS

The MAH submits bi-weekly reports on patients all over the world. Most reports are on non-EU patients. In every report, the MAH is required to discuss the EU patients separately.

In the EU, of the patients on Fabrazyme, approximately 4% was on a dose lower than 1 mg/kg/eow prior to the start of the supply shortage.

After a decline, the number of patients on Fabrazyme as well as the number of patients on the lowered dose seems to have stabilized. This is an indication that the recommendations are being followed to some extent and that no or a small number of new patients are being initiated on Fabrazyme.

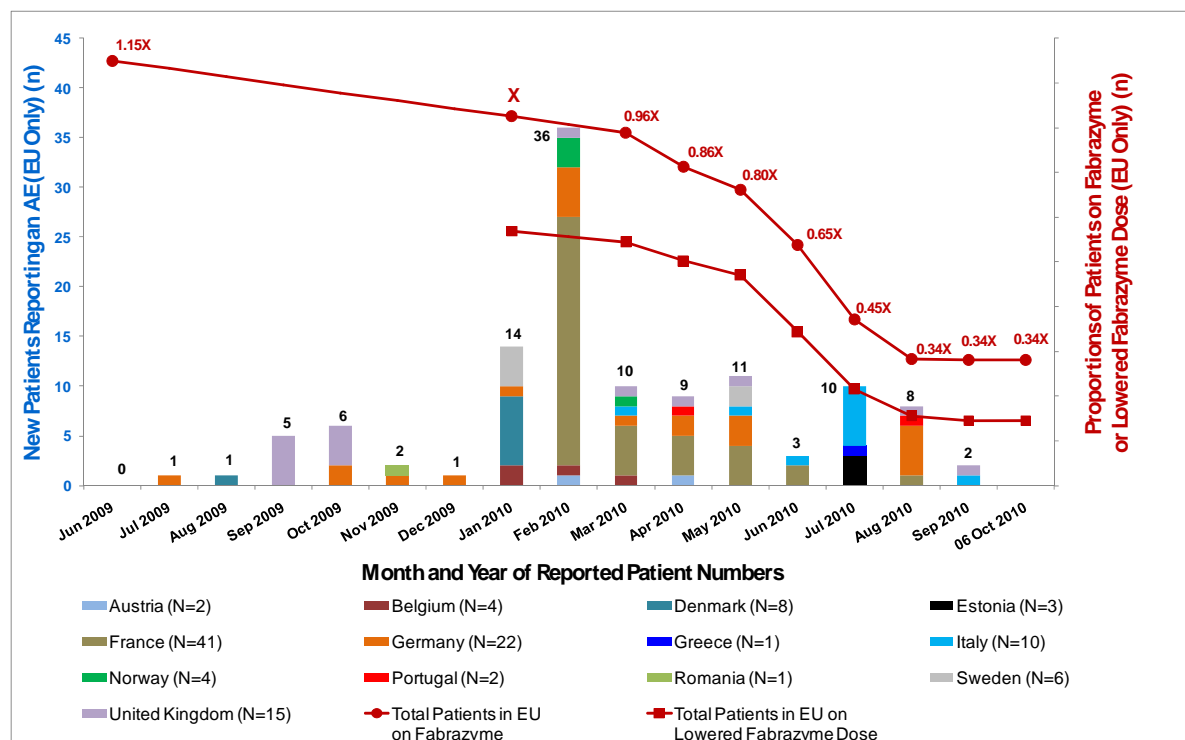
In the figure below, the bars indicate the numbers of reported AEs. The figure only presents the unique patients, so the real number of AEs is higher because for some patients there are more AE reports in time received. There appears to be a stabilisation in the number of AEs, suggesting that patients who still are on the lowered dose, are relatively stable and are not adversely affected by the use of the lowered dose.

See table 1 and figure 2 below.

Table 1: Estimated Percentage of Patients in the European Union on a Lower Dose

Estimated Number of:	January 2010	March 2010	April 2010	May 2010	June 2010	July 2010	August 2010	Sept. 2010	06 Oct. 2010
Patients on Fabrazyme*	x	0.96x	0.86x	0.80x	0.65x	0.45x	0.34x	0.34x	0.34x
Patients on 1 mg/kg/eow	26%	26%	25%	23%	31%	37%	37%	41%	41%
Pediatric patients on 1 mg/kg/eow	5%	5%	5%	5%	5%	6%	7%	7%	7%
Patients on 0.5 mg/kg/eow	32%	22%	23%	22%	21%	6%	13%	12%	12%
Patients on 0.3 mg/kg/eow	36%	47%	47%	50%	43%	51%	42%	40%	40%

*Note that x=total number of patients on Fabrazyme per January 2010 (exact number not disclosed for confidentiality reasons). In time, this number gradually decreases.

Figure 2 New Unique Patients Reporting AEs Assessed to be Potentially Suggestive of Clinical Deterioration on a Lowered Dose of Fabrazyme by Country, and Proportions of Patients on Fabrazyme and Lowered Doses of Fabrazyme (EU Patients Only) Since the Start of the shortage

* Bar graph data in Figure 1 represent the total number of unique patients by month who are new to the analysis of case reports assessed to be suggestive of potential clinical deterioration on a lowered dose of Fabrazyme. All patients new to the analysis during the current biweekly period are presented in that month. However, in subsequent reports, the patients will be listed in the month of the worldwide receipt date (WWRD) of their AE report. For example, if a case was initially reported with a WWRD in February 2010, but the data confirming that the patient was on a lowered dose were not received and medically reviewed until 20 September 2010, the case would be presented for the first time in the 16 September 2010 through 30 September 2010 biweekly report in the column for 16-30 September 2010. This presentation shows how many new unique patients from the EU are reporting AEs assessed to be suggestive of clinical deterioration on a lowered dose of Fabrazyme during the recent biweekly period. However, in subsequent reports, the case would be presented in the February 2010 column based on the initial WWRD to the safety database. Further, each unique patient is counted in Figure 1 only once. Therefore, if a patient reports one AE in September 2009 and another separate AE in March 2010, the patient will be included in the calculations for September 2009 only.

** The AEs received and medically reviewed after 30 September 2010 are beyond the scope of this document and will be presented in future reports.

There is a clear trend of increasing reports of (serious) AEs since the shortage. The higher the percentage of patients receiving the lowered dose, the higher the number of AEs reported. After the recommendations to switch to Replagal or to return to a higher dose when clinical deterioration appeared, this percentage decreased, as well the absolute number of reports. A subgroup of patients seems to be doing well on the lower Fabrazyme dose.

The MAH did not provide comparable data for the period before the shortage and concluded that based on the limited data available, it is not possible to ascertain whether more patients are having serious clinical events while on lowered doses of Fabrazyme, compared with earlier data from patients on a full dose of Fabrazyme.

However, the MAH did provide and compare quarterly data from Q3 2009 (see table 1). The percentage of AEs ascribed to the lowered dose increased steeply. After the increase in AEs seen from Q4 2009 to Q1 2010, the number of reported AEs from Q1 2010 to Q2 2010 appears to have been either stabilizing or decreasing.

Over time, increases have been seen in serious cardiac and nervous AEs and, to a lesser extent, in renal events, while a decrease, albeit less steep, has been seen in reported AEs related to pain/paresthesias.

The reported AEs are summarised in table 2. This table concerns data up to Q3 2010.

Note that this table presents worldwide data.

Table 2 Summary of Patients and Adverse Events Spontaneously Reported to Genzyme's Global Patient Safety & Risk Management Database That Were Received and Medically Reviewed from 25 June 2009 through 30 September 2010 and Assessed as Being Suggestive of Clinical Deterioration while on a Lowered Dose of Fabrazyme (selection of SOC's)

Adverse event category Preferred Term	Q3 2009 (N=21)		Q4 2009 (N=34)		Q1 2010 (N=89)		Q2 2010 (N=90)		Q3 2010	
	Events (n)	Patients (n)	Events (n)	Patients (n)	Events (n)	Patients (n)	Events (n)	Patients (n)	Events (n)	Patients (n)
Cardiac disorders (arrhythmias, cardiac failure, cardiac occlusion, MI)	1	1	1	1	13	12	14	14	11	10
Cerebrovascular-stroke	1	1	2	2	7	7	2	2	10	7
Fabry disease related pain	10	9	10	9	41	41	35	35	24	21
Gastrointestinal pain	2	2	5	5	3	3	5	4	7	7
Gastrointestinal diarrhoea	2	2	5	5	5	5	4	4	1	1
Renal disorders (renal failure, renal failure chronic)	-	-	-	-	6	6	4	4	9	9

The above data come from: a) Genzyme's "Report on Fabry Registry Patients who received Fabrazyme Dose reductions between 25 June 2009 and 05 August 2010 and Comparison to Spontaneous reports to Global Patients Safety and Risk Management Database" dated 23 September 2010; b) data from the third quarter 2010 (obtained from the biweekly reports 01-15 July; 16-31 July; 01-15 August; 16-31 August; 01-15 September; 16-30 September 2010.

Patients returning to higher dose or switched to Replagal

Some information was received on patients who had been switched to Replagal. However, the data is limited and no conclusions can be drawn from them.

There were also switches between Replagal and Fabrazyme prior to the Fabrazyme supply shortage.

GL-3 levels

There are some data available on GL-3 levels measured in patients before and after their dose lowering. These data do not show any clear trend.

IV. REVIEW OF DATA FROM FABRY REGISTRY

In the Fabry Registry, 410 patients were reported to be on lowered dose (US 59% and Europe 22%).

As of 5 August 2010, the Registry had enrolled a total of 3,681 Fabry patients (1,808 males and 1,873 females), irrespective whether or not they received enzyme replacement therapy.

Cerebrovascular events: The stroke incident rates have increased slightly since 25 June 2009 (from 0.63 (95% CI: 0.31–1.12) per 100 person years of follow-up to 1.32 (95% CI: 0.36–3.37).

Renal events: Since the previous Registry report, one new case of a renal event was reported (initiation of chronic dialysis). The incidence rate in these very small numbers did not increase during the shortage.

Cardiovascular events: The number of patients who had cardiovascular events after 25 June 2009 was small (N=3) and the observation period was short. Therefore, no conclusion can be made on whether or not there is any meaningful difference in the incidence of cardiovascular events in Fabrazyme-treated patients before and after 25 June 2009.

Neurologic peripheral pain, abdominal pain, diarrhoea: There have been consistent reports of a higher percentage of patients reporting peripheral pain, abdominal pain and diarrhoea on a daily basis after 25 June 2009, compared with the period before that date.

Globotriaosylceramide (GL-3) levels: The findings on the plasma GL-3 data are comparable with those in the spontaneous reporting; there is no apparent change.

Regarding urine GL-3 levels, six of the seven patients had lower levels post June 2009 compared with pre June.

V. CONSENSUS MEETING

On 4 and 9 October 2010, a consensus meeting of treating physicians was held. The purpose of that meeting was to reach consensus on the proper management of Fabry disease during the period of shortage of enzyme replacement therapy (ERT) and to come up with clear treatment recommendations for physicians during the shortage period of Fabrazyme (shortage of agalsidase beta and subsequent constraints in supply of agalsidase alfa). The aim was also to have the agreed treatment recommendations published in a scientific journal.

The EMA was present as an observer and the CHMP was informed of the outcomes of the meeting by the physicians' representative.

The CHMP took the outcome of this consensus group of experts into account.

VI. CONCLUSIONS

- There is a clear trend of increasing reports of (serious) AEs since the start of the shortage. The higher the percentage of patients receiving the lowered dose, the higher the number of AEs reported. After the recommendations to switch to Replagal or to return to a higher dose when clinical deterioration appeared, this percentage, as well the absolute number of reports, decreased. This provides a picture of more and more patients at risk from the lowered dose switching back to higher dose or to Replagal.
- A certain patient subgroup seems to have no obvious clinical effects due to the lowered dose.
- The safety data on the registry period June 2009 to 05 August 2010 confirm the trends as seen in the spontaneous reports. Due to its voluntary-based and periodic reporting, the Registry is somewhat 'behind' in time and this is reflected in the data. In the Registry so far the increases and decreases described above are still developing.

- Taking into account the potential for increased awareness of the supply shortage among healthcare providers which could potentially lead to reporting biases, the limitations of spontaneous reporting and the small number of reports, there is an increase in reporting of adverse events possibly due to the lowered dose. In the early stages of the shortage the main increases in AEs were related to pain/paresthesia events, while later on in the shortage period, the main increases were in serious cardiac events such as myocardial infarction, in serious nervous disorders such as stroke, and – possibly to a lesser extent – in renal disorders. There have been consistent reports of a higher percentage of patients reporting peripheral pain, abdominal pain and diarrhoea on a daily basis after 25 June 2009 (start of the shortage).
- **This pattern of adverse events resembles the natural, but accelerated, course of Fabry's disease.**
- The CHMP requests the MAH to include this important data on long-term low dosage use in the SPC in section 5.1. The MAH should provide wording stating that during the shortage period, spontaneous reports on the following adverse events (indicating a deterioration of the disease) were received: Fabry disease-related pain, paresthesia, diarrhoea, cardiac disorders as arrhythmias and myocardial infarction, nervous system disorders as stroke, and renal disorders as renal failure.
- A yet unexplained finding is that the plasma GL-3 levels show no apparent change before and after dose lowering. Data on the urine GL-3 levels are scarce; in six of the seven patients there was a lowering after dose lowering.